Modern Concepts of Cardiovascular Disease

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THE HEART IN PRIMARY SYSTEMIC AMYLOID DISEASE

Amyloidosis belongs to a large group of uncommon systemic diseases in which involvement of the heart may produce cardiac failure. Weiss and his coworkers have discussed the importance of an accurate etiologic classification of these obscure systemic diseases with cardiac involvement, because of the possibility of the use of specific therapy. By observing certain peculiarities of the cardiac and generalized effects of these rare processes, one may differentiate them from the more common types of cardiac disease.

Amyloidosis is a disease in which a foreign material, amyloid, is produced and deposited in certain tissues. It has been shown that amyloid consists of two protein and one polysaccharide fractions. It has been suggested that amyloid is a combination product, the result of union between some component of serum globulin and a fixed component of the vascular wall; or amyloid may represent deposits of excess globulin protein, since hyperglobulinemia may occur with amyloidosis. The occurrence of hyperglobulinemia and amyloidosis together often has been noted in plasma cell myeloma. The relationship of amyloid deposition to the allergic state acquired during chronic infections, particularly tuberculosis, has been stressed by Jaffe, but this possible etiologic sequence is less clear in the primary form of amyloid disease.

Amyloidosis has been classified as follows: (1) primary amyloidosis; (2) secondary amyloidosis; (3) amyloidosis associated with multiple myeloma and (4) tumor forming amyloidosis. Primary amyloidosis is rare, but is now a well-recognized entity. It differs from the more common secondary amyloidosis in several ways: (1) the absence of a specific etiologic factor, such as chronic suppuration, especially tuberculosis; (2) usually minimal or no deposition of amyloid in the liver, spleen, kidneys and adrenal glands, the sites of maximal deposition in secondary amyloidosis; (3) maximal deposition of amyloid in the heart, lungs, skin, mucous membranes and other tissues not ordinarily involved in secondary amyloidosis and (4) formation of nodular amyloid tumors.

Overlapping of the pathologic characteristics of the four types of amyloid disease has been observed, but the clinical diagnosis of primary systemic amyloidosis should be made easily, provided that the fairly characteristic symptoms, signs and patterns of amyloid distribution in the tissues are observed.

To date, 53 cases of primary systemic amyloidosis have been recorded in the literature. In 27 of these there was clinical evidence of congestive cardiac failure. In 22 of the 51 fatal cases, death was the result of cardiac failure, and in at least 18 of these, the clinical and pathologic evidence presented indicated that amyloid infiltration of the heart was responsible for the myocardial failure.

Amyloidosis might produce cardiac failure in several ways (1) by infiltration of the pulmonary vascular system with resulting chronic cor pulmonale, (2) by deposition of amyloid in the cardiac blood vessels, (3) by diffuse or localized nodular interstitial deposition of amyloid in the myocardium with or without secondary degeneration of the myocardial fibers, (4) by pericardial or endocardial deposition of amyloid, (5) by valvular deposition of amyloid with stenosis or insufficiency and (6) often by deposition in combination of several sites.

Clinical evidence of cardiac failure due to amyloid infiltration of the heart may be difficult to evaluate since the signs and symptoms may be produced by amyloid infiltration of the (1) lungs with chronic cor pulmonale, (2) trachea or (3) mediastinum, or by anemia which often is present. Furthermore, coronary atherosclerosis or hypertension may be complicating factors in the cardiac failure occurring in primary amyloid disease.

The signs and symptoms in the recorded cases of primary systemic amyloidosis were those of cardiac insufficiency and diminished blood flow to the myocardium. Since the majority of patients were in the older age group and had neither hypertension nor clinical evidence of valvular disease, the usual diagnosis was arteriosclerotic heart disease.

The diagnosis of primary amyloidosis may be suspected from the protean though somewhat uniform clinical picture which results from the widespread systemic distribution of amyloid substance. The systemic manifestations may point to an amyloid background for the cardiac disease.

A variety of cutaneous lesions have been described in primary amyloid disease. These include sclerodermic, papular, nodular or eczematous deposits. Some have a waxy appearance and are most frequently found about the eyelids or mucocutaneous junctions. These lesions of the skin plus those of the oral or vaginal mucosa, skeletal muscle, tongue, lymph nodes or periarticular tissues are easily accessible for biopsy. It should be stressed that a variety of amyloid stains be used on these biopsies, since the staining reactions of amyloid in the primary form of the disease are bizarre and variable.

Enlargement of the lymph nodes may be localized or generalized and may appear as a localized amyloid tumor. Macroglossia associated with dysphonia and dysphagia has been a frequent finding and has often been mistaken for malignant disease. The buccal and nasal mucosa, the larynx and trachea have been sites of infiltration, and even nasal hemorrhage and laryngeal obstruction have been described. Extensive skeletal muscular infiltration has produced the picture of myotonia or facial rigidity. Deposits in the posterior roots, sympathetic ganglia and peripheral nerves have occurred, but in the rare instances in which the central nervous system has been

involved the deposits have been limited to the intracranial vascular system.

Arthritis has been simulated, and involvement of the locomotor system has led to limitation of motion, disturbances in gait and pathologic fractures. Amyloid infiltration of the spinal marrow has produced collapse or narrowing of the vertebral bodies.

Amyloid involvement of the gastro-enteric tract has been a frequent finding in this group of cases and has been associated with a variety of abdominal signs and symptoms. Mucosal amyloid infiltration presumably was responsible for gastric ulceration in several instances, and massive hematemesis contributed to the death of several of these patients.

Ordinarily the liver, spleen and kidneys show minimal amyloid deposition in primary amyloidosis, but in some patients, the amyloid distribution has been similar to that seen in secondary amyloidosis. Although renal amyloid has been noted in more than half of the recorded cases of primary systemic amyloidosis, in only 3 was there a nephrotic syndrome and in only 5 was there terminal renal failure from renal amyloidosis. In 1 instance, amyloid infiltration of the liver was massive enough to produce icterus.

Pulmonary vascular infiltration may interfere with pulmonary blood flow and thus produce right ventricular hypertrophy and failure. In 1 recorded case, the pulmonary deposition of amyloid was so abundant that it produced a diffuse haziness of the pulmonary fields in the roentgenogram.

In addition to biopsy, the use of the intravenous Congo red test may be helpful in establishing the diagnosis of primary amyloidosis, though it was done in only 11 of the recorded cases. In only 5 were the results considered positive with percentages of dye absorbed from the blood at the end of one hour ranging from 60 to 100. In the 6 cases in which results were considered negative, the percentage of dye absorbed by the tissues in one hour ranged from 0 to 35.

Electrocardiographic studies were made in 16 of the 53 recorded cases of primary systemic amyloidosis. In those cases in which amyloid infiltration of the myocardium was extensive, low voltage was a prominent feature in the electrocardiographic record. In only 1 case was the P-R interval prolonged. In 1 there was a 2:1 heart block. Auricular fibrillation was present in 1 case and premature ventricular contractions were noted in 2. Axis deviation was more often to the left than the right. In at least 1 case, the abnormal electrocardiogram was the result of arteriosclerotic myocardial disease rather than amyloid. The electrocardiograms in this group of cases were usually interpreted as evidence of myocardial damage.

Cardiac amyloid rarely occurs in amyloidosis secondary to chronic infections, while primary amyloidosis generally is characterized by an atypical distribution of amyloid, especially with involvement of the heart. Thus cardiac amyloidosis was encountered in 43 of the 51 cases of primary amyloidosis in which necropsy reports were available.

The visceral pericardium has often been one site of cardiac deposition of amyloid in the primary form of the disease. These deposits may appear as small pearly flecks, or as larger translucent nodules. In one instance, the surface of the heart was covered by a grayish-gold, jelly-like membrane. From the published reports, it seems unlikely that amyloid deposits in the pericardium contribute to the production of cardiac failure.

Most of the cardiac amyloid has been distributed in the myocardium, and this seems most important in the mechanism of cardiac failure. Both auricular and ventricular walls may be thickened, and have been described as hard, grayish-tan, waxy or translucent, glossy and stiff or leathery, in those instances in which the myocardial amyloid was diffusely distributed. In some cases, the myocardial deposits appeared as opaque streaks or trabeculae, or as localized large or small nodular masses.

Most important in the mechanism of cardiac failure has been the diffuse interstitial amyloid infiltration of the myocardium. The extensive amyloid network appears to interfere greatly with the normal range of contraction and relaxation of the cardiac chambers. Narrow bands of amyloid deposited about individual myocardial fibers act as imprisoning rings or sheaths which sometimes invaginate into the cytoplasm of the myocardial cells.

The myocardial fibers thus surrounded may be compressed, degenerating or necrotic, and finally they disappear, leaving empty amyloid rings. These pericellular deposits may be continuous with amyloid in the blood vessels of the myocardium.

Endocardial and valvular deposits of amyloid are common; the former often extend from the myocardial amyloid masses. Valvular involvement is usually slight and only microscopically demonstrable. In some instances, these valvular deposits were larger and nodular or plaque-like. In 2 cases recorded in the literature, there were extremely abundant nodular translucent amyloid masses on all four cardiac valves. These produced thickening, rigidity and some degree of stenosis; it was considered in these instances that the valvular amyloid infiltration was responsible in part for the cardiac failure.

Amyloid deposits were found often in all layers of the walls of the blood vessels in the myocardium. The medium and small coronary arteries were involved more often than the veins, capillaries or arterioles. Vascular narrowing associated with this infiltration undoubtedly contributed to the failure of the myocardium in many of the cases.

While recovery from secondary amyloidosis may occur, regression of primary amyloidosis has not been apparent, since in only a few cases has an antemortem diagnosis been made by biopsy. Treatment of the primary form of the disease to date has been symptomatic and directed toward complications. The rate of progress of the disease is variable, but the course is long when compared to that of secondary amyloidosis. Duration of life from the onset of symptoms has varied from four months to sixteen years.

Jacobi and Grayzel have claimed that regression of amyloidosis secondary to tuberculosis resulted from the oral administration of a desiccated whole liver preparation; this should be evaluated in primary amyloid disease.

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